DEPARTMENT OF HEALTH AND HUMAN SERVICES

21 CFR Part 357

[Docket No. 81N-0060]

Orally Administered Drug Products for the Treatment of Fever Blisters for Over-the-Counter Human Use; Establishment of a Monograph

AGENCY: Food and Drug Administration, HHS.

ACTION: Advance notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing an advance notice of a proposed rulemaking that would establish conditions under which over-the-counter (OTC) orally administered drug products for the treatment of fever blisters are generally recognized as safe and effective and not misbranded. This notice is based on the recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products and is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments by April 5, 1982, and reply comments by May 5, 1982.

ADDRESS: Written comments to the Dockets Management Branch (formerly the Hearing Clerk's Office) (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Bureau of Drugs (HFD-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In accordance with Part 330 (21 CFR Part 330), FDA received on September 28, 1980 a report on OTC orally administered drug products for the treatment of fever blisters from the Advisory Review Panel on OTC Miscellaneous Internal Drug Products. FDA regulations (21 CFR 330.10(a)(6)) provide that the agency issue in the **Federal Register** a proposed order containing: (1) The monograph recommended by the Panel, which establishes conditions under which OTC orally administered drug products for the treatment of fever blisters are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph because the Panel determined that they would result in the drugs' not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph because the Panel determined that the available data are insufficient to classify these conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel.

The unaltered conclusions and recommendations of the Panel are issued to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The report has been prepared independently of FDA, and the agency has not yet fully evaluated the report. The Panel's findings appear in this document to obtain public comment before the agency reaches any decision on the Panel's recommendations. This document represents the best scientific judgment of the Panel members, but does not necessarily reflect the agency's position on any particular matter contained in it.

After reviewing all comments submitted in response to this document, FDA will issue in the **Federal Register** a tentative final monograph for OTC orally administered drug products for the treatment of fever blisters as a notice of proposed rulemaking. Under the OTC drug review procedures, the agency's position and proposal are first stated in the tentative final monograph, which has the status of a proposed rule. Final agency action occurs in the final monograph, which has the status of a final rule.

The agency's position on OTC orally administered drug products for the treatment of fever blisters will be stated initially when the tentative final monograph is published in the **Federal Register** as a notice of proposed rulemaking. In that notice of proposed rulemaking, the agency also will announce its initial determination whether the proposed rule is a major rule under Executive Order 12291 and will consider the requirements of the Regulatory Flexibility Act (5 U.S.C. 601-612). The present notice is referred to as an advance notice of proposed rulemaking to reflect its actual status and to clarify that the requirements of the Executive Order and the Regulatory Flexibility Act will be considered when the notice of proposed rulemaking is published. At that time FDA also will consider whether the proposed rule has a significant impact on the human environment under 21 CFR Part 25 (proposed in the **Federal Register** of December 11, 1979, 44 FR 71742).

The agency invites public comment regarding any impact that this rulemaking would have on OTC orally administered drug products for the treatment of fever blisters. Types of impact may include, but are not limited to, the following: Increased costs due to relabeling, repackaging, or reformulating; removal of unsafe or ineffective products from the OTC market; and testing necessary, if any. Comments regarding the impact of this rulemaking on OTC orally administered drug products for the treatment of fever blisters should be accompanied by appropriate documentation.

In accordance with § 330.10(a)(2), the Panel and FDA have held as confidential all information concerning OTC orally administered drug products for the treatment of fever blisters submitted for consideration by the Panel. All the submitted information will be put on public display in the Dockets Management Branch, Food and Drug Administration, after February 4, 1982, except to the extent that the person submitting it demonstrates that it falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality should be submitted to William E. Gilbertson, Bureau of Drugs (HFD-510) (address above).

FDA published in the **Federal Register** of September 29, 1981 (46 FR 47730) a final rule revising the OTC procedural regulations to conform to the decision in *Cutler* v. *Kennedy*, 475 F. Supp. 838 (D.D.C. 1979). The Court in *Cutler* held that the OTC drug review regulations (21 CFR 330.10) were unlawful to the extent that they authorized the marketing of Category III drugs after a final monograph had been established. Accordingly, this provision is now deleted from the regulations. The regulations now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process, before the establishment of a final monograph.

Although it was not required to do so under *Cutler*, FDA will no longer use the terms "Category I," "Category II," and "Category III" at the final monograph stage in favor of the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Categories I, II, and III because that was the framework in which the Panel conducted its evaluation of the data.

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally

recognized as safe and effective and not misbranded (monograph conditions) will be effective 6 months after the date of publication of the final monograph in the **Federal Register**. On or after that date, no OTC drug products that are subject to the monograph and that contain nonmonograph conditions, i.e., conditions which would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce. Further, any OTC drug products subject to this monograph which are repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to voluntarily comply with the monograph at the earliest possible date.

A proposed review of the safety, effectiveness, and labeling of oral OTC drugs by independent advisory review panels was announced in the **Federal Register** of January 5, 1972 (37 FR 85). The final regulations providing for this OTC drug review under § 330.10 were published and made effective in the **Federal Register** of May 11, 1972 (37 FR 9464). In accordance with these regulations, a request for data and information on all active ingredients used in OTC miscellaneous internal drug products was issued in the **Federal Register** of November 16, 1973 (38 FR 31696). (In making their categorizations with respect to "active" and "inactive" ingredients, the advisory review panels relied on their expertise and understanding of these terms. FDA has defined "active ingredient" in its current good manufacturing practice regulations (§ 210.3(b)(7), (21 CFR 210.3(b)(7))), as "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect." An "inactive ingredient" is defined in § 210.3(b)(8) as "any component other than an 'active ingredient.' " in the **Federal Register** of August 27, 1975 (40 FR 38179) a notice supplemented the initial notice with a detailed, but not necessarily all-inclusive, list of active ingredients in miscellaneous internal drug products to be considered in the OTC drug review. This list, which did not include ingredients in orally administered drug products for the treatment of fever blisters, was provided to give guidance on the kinds of ingredients for which data should be submitted. The notices of November 16, 1973, and August 27, 1975, informed OTC drug product manufacturers of their opportunity to submit data to the review at that time and of the applicability of the monographs from the OTC drug review to all OTC drug products.

Under § 330.10(a) (1) and (5), the Commissioner of Food and Drugs appointed the following Panel to review the information submitted and to prepare a report on the safety, effectiveness, and labeling of the active ingredients in these OTC miscellaneous internal products:

James L. Tullis, M.D., Chairman (appointed December 1979)
John W. Norcross, M.D., Chairman (resigned March 1979) Diana F. Rodriquez-Calvert, Pharm. D. (appointed July 1976)
Ruth Eleanor Brown, R.Ph. (resigned May 1976)
Elizabeth C. Giblin, M.N., Ed. D.
Richard D. Harshfield, M.D.
Theodore L. Hyde, M.D.
Claus A. Rohweder, D.O. (deceased April 13, 1979)
Samuel O. Thier, M.D. (resigned November 1975)
William R. Arrowsmith, M.D. (appointed March 1976)

Representatives of consumer and industry interests served as nonvoting members of the Panel. Eileen Hoates, nominated by the Consumer Federation of America, served as the consumer liaison until September 1975, followed by Michael Schulman, J.D. Francis J. Hailey, M.D., served as the industry liaison, and in his absence John Parker, Pharm. D., served. Dr. Hailey served until June 1975, followed by James M. Holbert, Sr., Ph. D. All industry liaison members were nominated by the Proprietary Association.

The following FDA employees assisted the Panel: Armond M. Welch , R.Ph., served as the Panel Administrator until July 1979, followed by John R. Short, R.Ph. Enrique Fefer, Ph. D., served as the Executive Secretary until July 1976, followed by George W. James, Ph. D., until October 1976, followed by Natalia Morgenstern until May 1977, followed by Arthur Auer until October 1978. Roger Gregorio served as the liaison for the Office of New Drug Evaluation beginning November 1978. Joseph Hussion, R.Ph., served as the Drug Information Analyst until July 1976, followed by Anne Eggers, R.Ph., M.S., until October 1977, followed by John R. Short, R.Ph., until July 1979.

In order to expand its scientific base the Panel called upon the following consultants:

Ralph B. D'Agostino, Ph. D. (statistics)
Lynn R. Brady, Ph. D. (pharmacognosy)
John A. Ulrich, Ph. D. (microbiology)

The Advisory Review Panel on OTC Miscellaneous Internal Drug Products was charged with the review of many categories of drugs, but due to the large number of ingredients and varied labeling claims, the Panel decided to review and publish its findings separately for several drug categories and individual drug products. The Panel presents its conclusions and recommendations for OTC orally administered drug products for the treatment of fever blisters in this document. The review of all other categories of miscellaneous internal drug products is being continued by the Panel, and its findings are being published periodically in the **Federal Register**.

The Panel was first convened on January 13, 1975 in an organizational meeting. Meetings at which orally administered fever blister drug products were discussed were held on the following dates: February 23 and 24, April 18 and 19, June 6 and 7, August 8 and 9, and September 28, 1980.

The minutes of the Panel meetings are on public display in the Dockets Management Branch (HFA–305), Food and Drug Administration (address above).

The following persons were given an opportunity to appear before the Panel at their own request to express their views on OTC orally administered drug products for the treatment of fever blisters:

Theodore R. Carski, M.D.
Terrence J. Thines, D.D.S.

No person who so requested was denied an opportunity to appear before the Panel to discuss orally administered drug products for the treatment of fever blisters.

The Panel has thoroughly reviewed the literature and data submissions, has listened to additional testimony from interested persons, and has considered all pertinent data and information submitted through September 28, 1980 in arriving at its conclusions and recommendations for OTC orally administered drug products for the treatment of fever blisters.

In accordance with the OTC drug review regulations in § 330.10, the Panel reviewed OTC orally administered drug products for the treatment of fever

blisters with respect to the following three categories:

Category I. Conditions under which OTC orally administered drug products for the treatment of fever blisters are generally recognized as safe and effective and are not misbranded.

Category II. Conditions under which OTC orally administered drug products for the treatment of fever blisters are not generally recognized as safe and effective or are misbranded.

Category III. Conditions for which the available data are insufficient to permit final classification at this time.

The Panel reviewed eight active ingredients in orally administered drug products for the treatment of fever blisters and classified no ingredients in Category I, five ingredients in Category II, and three ingredients in Category III.

I. Submission of Data and Information

A. Submissions by Firm

Pursuant to notices published in the **Federal Register** of November 16, 1973 (38 FR 31696) and August 27, 1975 (40 FR 38179), Hynson, Westcott, and Dunning, Baltimore, MD 21201, was the only firm to make submissions (Lactinex tablets and granules) for OTC orally administered drug products for the treatment of fever blisters.

B. Ingredients Reviewed by the Panel

1. *Labeled ingredients contained in marketed products submitted to the Panel.*

Lactobacillus acidophilus
Lactobacillus bulgaricus

2. *Other ingredients.* In addition to those ingredients included in the products submitted to the Panel, the Panel reviewed the ingredient lysine and the product Herp-eze Tablets (Anjonic, Inc., Hawthorne, CA 90250), both of which were brought to the Panel's attention by FDA's Office of Compliance, Bureau of Drugs. The labeled ingredients contained in these products are as follows:

Acetaminophen
Caffeine
Chlorpheniramine maleate
Lysine
Phenylephrine hydrochloride
3,3-Bis (*p*-hydroxyphenyl) Phthalide

C. Classification of Ingredients

1. *Active ingredients.*
Lactobacillus acidophilus
Lactobacillus bulgaricus

Lysine (lysine hydrochloride)

2. *Other ingredients.* The Panel was neither able to locate nor is it aware of any data demonstrating the safety and effectiveness of the following OTC ingredients when used as orally administered drug products for the treatment of fever blisters. The Panel, therefore, classifies these ingredients as Category II for this use, and they will not be reviewed further in this document.

Acetaminophen
Caffeine
Chlorpheniramine maleate
Phenolphthalein (3,3-Bis (*p*-hydroxyphenyl) Phthalide)
Phenylephrine hydrochloride

D. Referenced OTC Volumes

The "OTC Volumes" cited throughout this document include submissions made by interested persons in response to the call-for-data notices published in the **Federal Register** of November 16, 1973 (38 FR 31696) and August 27, 1975 (40 FR 38179). All of the submitted information included in these volumes, except for those deletions which are made in accordance with the confidentiality provisions set forth in § 330.10(a)(2), will be put on public display after February 4, 1982, in the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishes Lane, Rockville, MD 20857.

II. General Statements and Recommendations

A. Definitions of Terms

For the purpose of this document, the Panel agreed upon the following definitions:

1. *Aphthous stomatitis.* Canker sore.
2. *Aphthous ulcer.* Canker sore.
3. *Canker sores.* Sores which occur on the mucous membranes of the oral cavity (often the movable areas) and may be associated with a variety of viruses, bacteria, or fungi. They are characterized by small whitish ulcerative lesions surrounded by a red border.
4. *Cold sores.* Fever blisters.
5. *Fever blisters.* Recurrent sores on the lips and other areas around the mouth, usually caused by herpes simplex virus. They are characterized by local tissue swelling followed by inflammation which evolve into vesicular eruptions, and then crust and fade.
6. *Vesicular eruption.* A small blister containing fluid.

B. General Discussion

Although this document deals with orally administered drug products for the treatment of fever blisters (cold sores), the Panel believes that there is sufficient confusion among consumers in differentiating between feaver blisters and canker sores (aphthous stomatitis or aphthous ulcer) to warrant a discussion of both in this "General Discussion." The discussions regarding effectiveness will center on relieving the discomfort of fever blisters, not on shortening the duration of the episode, because it is difficult from the literature description of the disease to determine the time of the onset of symptoms.

Fever blisters or "cold sores." generally caused by herpes simplex virus, are recurrent sores on the lips and other areas around the mouth that may cause discomfort and annoyance to millions of Americans (Ref. *1*). Usually, the initial manifestation of the virus occurs in children under 5 years of age as a primary infection. This infection is frequently so mild it goes unnoticed by the individual. Later in a person's life, the virus, having been dormant in the body, may be reactivated when provoked by nonspecific stimuli, such as colds, exposure to sunlight, menstruation, a variety of common bacterial and viral infections, fever, and neurosurgical operations (Ref. *1, 2,* and *3*). Psychological stress is also accepted as capable of provoking the virus. The viral reactivation manifests itself in the form of localized vesicular eruptions, characteristically involving the mouth, nose, or external genitalia and sometimes other areas. During the first few days, the virus can be cultivated from the vesicular fluid (Refs. *1* and *4*), or transmitted by close person-to-person contact (Refs. *5* and *6*). The primary vesicles usually evolve, crust, and fade in 1 week, with secondary healing sometimes taking 2 weeks. Recurrence, ofter at the same site, is common, although some persons who harbor the virus throughout their lifetime may never have the skin lesions.

The OTC drug products for treating fever blisters consist of internal and external medications. Only those which are internally administered will be considered in this document. Externally applied preparations will be considered by the Advisory Review Panel on OTC Miscellaneous External Drug Products.

The Panel recognizes that canker sores in the mouth commonly have been confused with fever blisters as being of similar herpetic origin. Although some canker sores are of such origin, they generaly are entirely different diseases. Canker sores are of diverse etiology (cause), including certain viruses, bacteria, and fungi. Like fever blisters, they are generally painful and recurrent. Canker sores are characterized by small whitish ulcerative lesions surrounded by a red border (Ref. *7*) and are often found on the movable areas of the lining of the mouth (e.g., the inner lining of the cheeks and lips, the tongue, and the soft

palate) (Ref. *1*). They usually appear initially in persons between 10 and 20 years of age, but may appear as early as 2 years of age (Ref. *1*). Canker sores can occur later in life and may be of spontaneous origin or may be secondary to other disease states, including immune suppression. If left untreated, canker sores usually heal in 10 to 14 days (Ref. *1*). The ulcers tend to recur when the patient has experienced local injury (e.g., scratch of a toothbrush bristle), has an allergic reaction (e.g., following ingestion of certain foods), has an endocrine-associated condition (e.g., menstruation), or is subject to emotional stress (Refs. *1* and *7*). Poor oral care may also be cause of canker sores.

Because of the varied appearance of the lesions and the variability of the clinical symptoms, canker sores have been given many names, and many drug products have been tried for treating them. Most of these are topicaly applied and include dyes, resins such as myrrh, hydrocolloid films such as aloe, astringents and protein precipitators such as alum, and antibacterials such as hydrogen peroxide.

The treatment of canker sores with oral wound cleansers was previously reviewed by the Advisory Review panel on OTC Dentifrice and Dental Care Drug Products in its report, published in the **Federal Register** of November 2, 1979 (44 FR 63270) on OTC Oral Mucosal Injury Drug Products. That Panel concluded that oral wound cleansers should not be used to treat canker sores because the term "canker sore" is vague to consumers, the condition cannot be self-diagnosed and is serious, and self-treatment may delay diagnosis (44 FR 63283). The Advisory Review Panel on OTC miscellaneous Internal Drug Products has reviewed this conclusion and believes thaat, although canker sores may be self-diagnosable, their cause cannot be determined by the consumer, and therefore thay cannot be self-treated appropriately. This is because, although canker sores are not dangerous in themselves, they may be related to a serious condition, and an ingredient might be shown to be effective for one type of canker sore but not for others. One then takes the chance that a serious condition may go untreated, or, at best, treatment will be delayed. Therefore, the Panel will not review further the treatment of canker sores.

References

(*1*) "Canker Sores and Fever Blisters," United States Department of Health, Education, and Welfare, DHEW Publication No. (NIH) 79–247, 1979.

(*2*) Cruickshank, R., "Medical Microbiology," 11th Ed., The Williams and Wilkins Co., Baltimore, pp. 382–386, 1965.

(*3*) Wilson, G. S., and A. A. Miles, "Topley and Wilson's Principles of Bacteriology, Virology and Immunity, 6th Ed., Vol. II, The Williams and Wilkins Co., Baltimore, pp. 2414–2422, 1975.

(*4*) Freeman, B. A., "Burrows Textbook of Microbiology," 21st Ed., W. B. Saunders Co., Philadelphia, pp. 973–976, 1979.

(*5*) Joklik, W. K., and H. P. Willett, "Zinsser Microbiology," 16th Ed., Appleton-Century-Crofts, New York, pp. 944–947, 1976.

(*6*) Davis, B. D., et al., "Microbiology," Harper and Row, New York, pp. 1238–1244, 1967.

(*7*) "Dorland's Illustrated Medical Dictionary," 25th Ed., W. B. Saunders, Philadelphia, 1974, s. v. "stomatitis, aphthous."

C. Labeling

The Panel has carefully reviewed the submitted labeling claims for products promoted as orally administered drug products for the treatment of fever blisters and has classified them as Category I, Category II, or Category III. The Panel realizes that other terms may be developed to express the same Category I indications. However, only those indications and warnings listed under Category I are generally recognized to be acceptable at this time.

In order for any labeling to be acceptable, it must include (1) the indiction(s) for use, (2) pertinent warnings and contraindications, and (3) clear directions for use that include the recommended dosage.

The Panel believes that all labeling should be clear, concise, easily read, and understood by most consumers. It has followed this concept in the development of all Category I labeling. The Panel also is concerned about the size and color of the print used in labeling of these and all OTC drug products and recommends that the manufacturers make the necessary effort to design labeling which is legible.

One of the functions of this Panel is to attempt to eliminate inadequate labeling claims. Some of the labeling on currently marketed orally administered drug products for the treatment of fever blisters is misleading or unsupported by scientific data. Accordingly, such labeling has been placed in Category II.

The indications for use should be simply and clearly stated; the directions for use should provide enough information for safe and effective use of the product.

The Panel believes that if two ingredients are indistinguishable with regard to effectiveness, it is misleading to claim superiority for one of the ingredients. The Panel understands that its function is not to compare various ingredients in order to determine the OTC drug of choice, but to determine only safety and effectiveness for active OTC miscellaneous internal ingredients, as well as proper dosage ranges, warnings, and contraindications.

Misleading or undocumented claims, such as "for the relief of the discomfort of sun blisters," and colloquial or provincial expressions that do not have meaning to most people must not be used. In the labeling, effectiveness shall not be relate to the physical characteristics of the product, except as those characteristics may related to the action of the active ingredients.

The Panel is aware of the current OTC labeling regulation dealing with warning statements (§ 330.1(g)). The Panel concurs with the warning, "Keep this and all drugs out of the reach of children," and believes that it should be incorporated in the labeling for orally administered drug products for the treament of fever blisters. However, the Panel recommends that the other warning statement required by § 330.1(g), "In case of accidental overdose, seek professional assistance or contact a Poison Control Center immediately," be deleted because no toxicity has been demonstrated for ingredients used in these products.

In addition, the Panel recommends that the drug product labeling contain instructions for the most effective use of the product. These instructions should be displayed prominently on all package labeling.

The Panel recommends that the label should contain a listing of all ingredients, clearly indicating which are active and which are inactive. Active ingredients should be listed by their established names, and the label should state the quantity of the active ingredient included in a single dose.

III. Orally Administered Drug Products for the Treatment of Fever Blisters

A. *Category I Conditions*

The following are Category I conditions under which OTC orally administered drug products for the treatment of fever blisters are generally recognized as safe and effective and are not misbranded.

1. *Category I active ingredients.* None.

2. *Category I labeling.* Although the Panel has not classified any ingredients in Category I, it recommends the following Category I labeling for OTC orally administered drug products for the treatment of fever blisters, as well as any specific labeling discussed in the individual ingredient statement, in the event that any ingredients that are in

Category III should be reclassified as Category I. The product labeling relating to fever blisters should contain a statement under the heading "Indications" that is limited to the phrase "For the relief of the discomfort of fever blisters (cold sores)."

B. Category II Conditions

The following are Category II conditions under which OTC orally administered drug products for the treatment of fever blisters are not generally recognized as safe and effective or are misbranded.

1. *Category II active ingredients.* The ingredients which the Panel has classified as Category II are included elsewhere in this document. (See part I. paragraph C.2. above—Other ingredients.)

2. *Category II labeling.* The Panel concludes that the following labeling claims for orally administered drug products for the treatment of fever blisters are misleading or unsupported by scientific data. Therefore, the claims listed below and other related terms are classified as Category II labeling:

a. "For the relief of discomfort of sun blisters."

b. "Useful for fever blisters of herpetic origin."

c. "Arrests the symptoms associated with cold sores and sun blisters on the lips."

C. Category III Conditions

The following are Category III conditions for which the available data are insufficient to permit final classification at this time.

1. *Category III active ingredients.*

Lactobacillus acidophilus
Lactobacillus bulgaricus
Lysine (lysine hydrochloride)

a. *Lactobacillus acidophilus and Lactobacillus bulgaricus.* The Panel has reviewed the use of orally administered live *Lactobacillus acidophilus* and *Lactobacillus bulgaricus* for the treatment of fever blisters (herpetic origin) and concludes that when these ingredients are used separately or in combination they are safe for OTC use in the dose noted below, but data are insufficient to demonstrate effectiveness for this use.

The marketed preparation is a mixture of these two organisms and is prepared from fermented milk cultures which are dried in a lactose-enriched medium and marketed in such a form. There is also a preparation on the market which contains the *Lactobacillus acidophilus* alone.

Being living organisms rather than single chemical compounds, the active ingredients, *Lactobacillus acidophilus* and *Lactobacillus bulgaricus*, are not recognized as official by such compendia as the U.S. Pharmacopeia and the National Formulary. Therefore, there are no compendial standards to which these ingredients must conform. The Panel is concerned that identification of these strains of bacteria by their name alone is not sufficiently specific to insure that all products containing these organisms will be equivalent in terms of safety and effectiveness. Therefore, the Panel has chosen to specify these ingredients further by using the identification number assigned to them by the American Type Culture Collection (ATCC): *Lactobacillus acidophilus* (ATCC 4962) and *Lactobacillus bulgaricus* (ATCC 33409).

(1) *Safety.* The use of *Lactobacillus acidophilus* and *Lactobacillus bulgaricus* has been reviewed by the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products as published in the **Federal Register** of March 21, 1975 (40 FR 12902), and that Panel concluded that these ingredients are safe in amounts taken orally in antidiarrheal preparations (40 FR 12931). The OTC Miscellaneous Internal Drug Products Panel agrees with the Advisory Review Panel on OTC Laxative, Antidiarreal, Emetic, and Antiemetic Drug Products and concludes that *Lactobacillus acidophilus* and *Lactobacillus bulgaricus* (separately or in combination) are safe for OTC use and recommends the manufacturer's suggested dose of up to 4 grams (g) per day in divided doses (Ref. *1*). This is equivalent to approximately 400,000,000 organisms.

Because many people are sensitive to milk products and because this preparation may contain residual milk products, a warning regarding possible sensitivity should be included.

(2) *Effectiveness.* A 1961 study by Abbott (Ref. *2*) reported the use of a live mixture of *Lactobacillus acidophilus* and *Lactobacillus bulgaricus* in treating 78 subjects. Forty-six children with acute generalized herpetic gingivostomatitis (virus infection of the gums) were cured within 6 days of treatment (untreated usually taking 14 to 21 days). Ten adults with histories of recurrent herpes simplex lip lesions (fever blisters) were treated at the onset of burning or itching but before any vesicular eruption, and in no cases did the eruptions occur. The study was uncontrolled and not blinded.

In 1965, Rapoport and Levine (Ref. *3*) reported the treatment of pain of herpetic (fever blisters) and aphthous stomatitis oral ulcerations with *Lactobacillus acidophilus* and *Lactobacillus bulgaricus* in 40 cases with positive results in 38 cases. Pain was relieved in 38 patients within 48 hours, and lesions disappeared within 5 days in 36 patients, which the authors considered to be "a statistically notable number of remissions." From the data given it is impossible to separate the herpetic stomatitis lesions from the aphthous stomatitis. No placebo controls or blinding were used in this study, and the findings were reported by the subjects to the investigator by telephone.

In 1963, a study was reported by Scott (Ref. *4*) in which 44 cases of oral lesions were treated using *Lactobacillus acidophilus*. The lesions consisted of aphthous stomatitis, cheilosis (lesions at the corner of the mouth), and herpes simplex infections (fever blisters), but from the data given it is impossible to separate the herpes simplex infection cases from the other conditions. Thirty-seven of the patients (84 percent) responded positively to the treatment within "a few days." The study was uncontrolled and not blinded.

A 1964 study by Unfug (Ref. *5*) at Colorado State University using *Lactobacillus acidophilus* and *Lactobacillus bulgaricus* involved 61 students, some with acute fever blisters and others with canker sores. The study was double-blinded and placebo-controlled, but not completed, and it did not show a significant difference between the two treatment groups (45 percent success in drug group vs. 31 percent success in placebo group). Details of this study were not available, but it is known that the study was prematurely terminated due to a lack of cooperation from the students, a lack of a virology facility, and a lack of interest among the physicians covering the student health service.

In 1963, Weekes (Ref. *6*) studied the effect of *Lactobacillus acidophilus* and *Lactobacillus bulgaricus* on 174 patients. Sixty-four were identified as having herpes simplex labialis (fever blisters) and 97 as having aphthous stomatitis. The remainder had dendritic ulcers or herpes progenitalis. Ninety-five percent of those with herpes simplex labialis were reported to have favorable results (healing or improvement in 1 to 4 days). However, the Panel criticizes the study because it has no placebo control nor was it a double-blind study.

An incomplete study by Weekes (Ref. *7*) from 1966 to 1968, which was double-blinded and placebo-controlled and involved 106 patients, showed no significant difference between placebo and a preparation containing *Lactobacillus acidophilus* and

Lactobacillus bulgaricus in treating fever blisters and canker sores (64 percent success rate vs. 59 percent for placebo). A subsequent expansion of this study to 178 cases (72 with no case report forms) showed the treated group to have "significantly superior" results. This unpublished study was unsatisfactory in that the treatment assignments were not completely randomized, completed case report forms were available on only 106 subjects, and the followup time to judge the effect of the treatment was inconsistent (2 days or longer). From the data given it is impossible to separate the results of the fever blister and canker sore cases.

A double-blind, placebo-controlled parallel sample study by Gertenrich and Hart (Ref. *8*) involving 80 mentally retarded subjects showed no significant differences between *Lactobacillus acidophilus* and a placebo in healing time for oral lesions. Only 10 percent of the lesions observed in this study were fever blisters; the other 90 percent were canker sores. Because of the small number of fever blister cases, a statistical analysis could not be adequately performed. Each patient was examined and the lesions photographed every 3 days from the time of onset through a 10-day period. In contrast to other studies in general the lesions were unhealed after at least 4 days, and almost half had incomplete hearing after 10 days.

A presentation was made by Carski and Thimes (Ref. *9*) to the Panel of a double-blind, placebo-controlled, crossover study undertaken by Thines and Uthman (Ref. *10*) at the State University of New York at Buffalo School of Dentistry. Twenty-five students with histories of recurrent herpes simplex infections were treated with *Lactobacillus acidophilus* and *Lactobacillus bulgaricus*. Only 16 students completed the treatment. Based on the subjective evaluation of each episode by the observer and subject, 75 percent reported improvement during the episode that was treated with the *Lactobacillus acidophilus* and *Lactobacillus bulgaricus* combination, whereas only 31 percent of the subjects reported episode improvement under the influence of the placebo. Improvement was based on comparison with prestudy episodes. The differences between this percentage of improvements is statistically significant at a level greater than 0.05 but less than 0.10. Further, the mean duration between episodes for those subjects who were first on the drug was 105 days, and the mean duration between episodes was 53 days for those subjects who were first on the placebo. The difference between the mean durations was tested for statistical significance level by using the Wilcoxon Rank test, and the difference attained a significance level between 0.05 and 0.10. While this study indicates that the lactobacillus therapy had a positive effect, it had a large dropout rate (36 percent); it employed as an effectiveness measure a comparison prestudy episodes, rather than a direct comparison with with the crossover episodes, and it did not achieve the usual acceptable level of 0.05 or less of statistical significance to establish effectiveness. Therefore, the Panel does not believe the study is sufficient to establish effectiveness.

Three other studies were reviewed, but none of them contained an evaluation of fever blisters, which is the primary subject of this document.

The Panel concludes that the studies reviewed are merely indicative of possible effectiveness of *Lactobacillus acidophilus* and *Lactobacillus bulgaricus* in treating fever blisters. Well-designed and well-controlled studies are still needed to definitely establish effectiveness of these ingredients.

Although the mechanism of action of *Lactobacillus acidophilus and Lactobacillus bulgaricus is not understood, an unpublished study presented in a submission to the Panel by McCuen, Holman, and Cook (Ref. 11)* suggests that these organisms when given to human volunteers in multiple doses, induce in human saliva the ability to inhibit *Herpesvirus hominis*, type I. The results of this study indicated that further clinical study should be encouraged. A single-dose study by McCuen (Ref. *12*) did not demonstrate any indication of salivary inhibition of herpes virus.

The Panel considers *Lactobacillus acidophilus* (ATCC 4962) and *Lactobacillus bulgaricus* (ATCC 33409) similar enough in their taxonomy and action to recommend that the combination of these ingredients be exempt from FDA's combination policy regulation (21 CFR 330.10(a)(4)(iv)). Therefore, clinical studies of the two ingredients together would be acceptable, i.e., one would not have to demonstrate an advantage of one ingredient over the other to substantiate the combination. However, a claim for either ingredient alone would require demonstration of effectiveness by separate studies.

The Panel concludes that available data suggest that *Lactobacillus acidophilus* and *Lactobacillus bulgaricus* (separately or in combination) may be effective in treating fever blisters, but data are insufficient to permit a final determination. The Panel, therefore, recommends that these ingredients (separately or in combination) be tested according to the testing guidelines to determine their effectiveness as orally administered drugs for the treatment of fever blister. (See part III. paragraph D. below—Data Required for Evaluation.)

Because it is necessary that these bacteria be alive in order to perform their intended function, they must be kept refrigerated at temperatures between 36° and 46° F. A statement to this effect should be required on the labeling.

(3) *Proposed dosage.* The Panel concludes that *Lactobacillus acidophilus* and *Lactobacillus bulgaricus* (separately or in combination) are safe for OTC use in a dose of up to 4 g per day in divided doses. This is equivalent to approximately 400,000,000 organisms.

(4) *Labeling.* The Panel recommends Category I labeling for orally administered drug products for the treatment of fever blisters. (See part III. paragraph A.2. above—Category I labeling.) In addition, the Panel recommends the following statements be added for products containing *Lactobacillus acidophilus* and *Lactobacillus bulgaricus:*

(i) *Warning.* "Do not use this product if you are sensitive to milk products."

(ii) *Other required statement.* "Refrigerate between 36° and 46° F."

(5) *Evaluation.* The Panel concludes that *Lactobacillus acidophilus* and *Lactobacillus bulgaricus* (separately or in combination) are safe for OTC use in the dose noted above, but data are insufficient at this time to make final determination regarding general recognition of effectiveness. The Panel recommends that adequate testing be performed according to the testing guidelines to determine whether these ingredients are effective in treating fever blisters. (See part III. paragraph D. below—Data Required for Evaluation.)

References

(*1*) OTC Volume 170052.

(*2*) Abbott, P. L., "Viable Mixture of Lactobacillus Acidophilus and Bulgaricus in Treatment of Herpetic and Aphthous Stomatitis," *Journal of Oral Surgery, Anesthesia, and Dental Service*, 19:310–312, 1961.

(*3*) Rapoport, B. S., and W. I. Levine, "Treatment of Oral Ulceration with Lactobacillus Tablets," *Oral Surgery, Oral Medicine, Oral Pathology*, 20:591–593, 1965.

(4) Scott, P. H., "Preliminary Report on Lactobacillus Acidophilus and Its Therapeutic Application for Oral Lesions," *New York State Dental Journal*, 29:19–24, 1963.

(5) Unfug, H., untitled clinical study contained in OTC Volume 170052 (Section V, pp. 14–16).

(6) Weekes, D. J., "Management of Herpes Simplex with a Viro-Static Bacterial Agent," reprinted from *E.E.N.T. Digest*, Volume 25, Number 12, 1963, as attachment to letter to Panel Administrator from Dr. Theodore R. Carski, April 25, 1980, in Panel Administrator's File, Volume 171API.

(7) Weekes, D. J., untitled clinical study contained in OTC Volume 170052 (Section V, pp. 17–18).

(8) Gertenrich, R. L., and R. W. Hart, "Treatment of Oral Ulcerations with Bacid *(Lactobacillus acidophilus)*," *Oral Surgery, Oral Medicine, and Oral Pathology*, 30:196–200, 1970.

(9) Presentation by Carski and Thines to the Panel included in the Summary Minutes of the 35th meeting of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products held on April 18–19, 1980.

(10) Uthman, A. A., and T. Thines, "Clinical Evaluation of the Effect of Lactinex Administration for the Treatment of Recurrent Herpes," in OTC Volumes 170185.

(11) McCuen, P. J., D. A. Holman, and D. L. Cook, "Evaluation of the Effect of Lactinex Administration on the Ability of the Saliva from Human Volunteers to Inhibit Herpesvirus," contained in OTC Volume 170180 (Section IV).

(12) McCuen, P. J., "Evaluation of the Effect of Single Dose Lactinex Administration on the Ability of the Saliva from Human Volunteers to Inhibit Herpesvirus," contained in OTC Volume 170180 (Section V).

b. *Lysine (lysine hydrochloride).* The Panel concludes that lysine hydrochloride is safe in the dose noted below, but data are insufficient to demonstrate its effectiveness in treating fever blisters.

(1) *Safety.* Lysine is an essential amino acid present in protein derived from many food stuffs. The adult human requires a daily ingestion of 0.4 to 0.8 g daily; for optimum health, however, a larger "safe intake" of 1.6 g has been recommended (Ref. *1*). Infants and children require a much larger intake in proportion to their weight for adequate growth. The Panel has found no information on toxic dosages of lysine, but was informed that a dermatologist in the Southwest United States prescribes 3 g per day; no mention was made of any toxic effects (Ref. *2*).

(2) *Effectiveness.* An in vitro study by Tankersly (Ref. *3*) demonstrated that lysine exerted an inhibitory effect on herpes simplex virus multiplication in human cells grown in tissue culture. The ratio of lysine to arginine in the culture medium seemed to be important. Kagan (Ref. *4*), in 1974, administratered 390 milligrams (mg) of *L*-lysine orally to 10 patients at the first onset of symptoms of oral (8 patients) or vulvar (2 patients) herpetic lesions and observed rapid resolution of these lesions. A further study by Griffith, Norins, and Kagan (Ref. *5*) found that the continuous ingestion of 312 to 1,200 mg of *L*-lysine (administered as *L*-lysine monohydrochloride) daily in single or multiple doses (for 2 months to 3 years) by 45 patients suffering from recurrent herpetic lesions resulted in suppression of the lesions in 40 patients. Results showed that new vesicles failed to appear, healing was more rapid, frequency of recurrences was reduced, and there was a "disappearance of pain overnight." This study was not controlled.

Modern Medicine cities Pipkin as claiming that a 3-g per day dose of lysine is more effective than the lower doses tested by other investigators (Ref. *2*).

The Panel realizes that neither of the two following studies pertain to the relief of fever blister discomfort, but are referenced herein for completeness. A double-blinded, placebo-controlled, randomized study was conducted by Milman, Scheibel, and Jessen (Ref. *6*) using 500 mg of *L*-lysine monohydrochloride twice daily in 119 patients. They found lysine to have no effect on the rate of healing, the appearance of the lesion, or the interval between recurrance of oral herpetic lesions. In a 24-week double-blind, placebo-controlled study by Milman, Scheibel, and Jessen (Ref. *7*) involving 65 patients and the same dosage of lysine as in the last study, lysine had no significant prophylactic effect, either on the duration or on the frequency of recurrances of herpes simplex labialis. However, in this study significantly more patients were recurrence-free (i.e., that subset of patients who had no recurrences during the study) during the lysine treatment than during the placebo treatment (18 vs. 8 with a p of 0.05). This finding suggests an effect of lysine on some patients.

The Panel concludes that the effectiveness of lysine hydrochloride in amelioration or prevention of herpes simplex lesions is unproven.

(3) *Proposed dosage.* The Panel concludes that lysine hydrochloride is safe for OTC use in a dose of up to 3 g daily.

(4) *Labeling.* The Panel recommends Category I labeling for OTC orally administered drug products for the treatment of fever blisters. (See part III. paragraph A.2. above—Category I labeling.)

(5) *Evaluation.* The Panel concludes that lysine hydrochloride is generally recognized as safe for OTC use in a dose of up to 3 g daily, but data are insufficient to demonstrate its effectiveness in treating fever blisters. The Panel recommends that adequate testing be performed according to the testing guidelines set forth below to determine whether lysine hydrochloride is effective in treating fever blisters. (See part III. paragraph D. below—Data Required for Evaluation.)

References

(1) Best, C. H., and N. B. Taylor, "The Physiological Basis of Medical Practice," 8th Ed., Williams and Wilkins Co., Baltimore, p. 1319, 1966.

(2) Anon., "News Fronts," *Modern Medicine*, 48:17, 1980.

(3) Tankersly, R. W., "Amino Acid Requirements of Herpes Simplex Virus in Human Cells," *Journal of Bacteriology*, 87:609–613, 1964.

(4) Kagan, C., "Lysine Therapy for Herpes Simplex," *Lancet*, 1:137, 1974.

(5) Griffith, R. S., A. L. Norins, and C. Kagan, "A Multicentered Study of Lysine Therapy in Herpes Simplex Infection," *Dermatologica*, 156:257–267, 1978.

(6) Milman, N., J. Scheibel, and O. Jessen, "Failure of Lysine Treatment in Recurrent Herpes Simplex Labialis," *Lancet*, 2:942, 1978.

(7) Milman, N., J. Scheibel, and O. Jessen, "Lysine Prophylaxis in Recurrent Herpes Simplex Labialis: a Double-Blind, Controlled Crossover Study," *Acta Dermato Venereologica*, 60:85–87, 1980.

2. *Category III labeling.* The Panel concludes that available data are insufficient to demonstrate the effectiveness of orally administered drug products for the treatment of fever blisters on the duration of the episode and places the following claim in Category III: "Will shorten the duration of fever blisters (cold sores) if taken at the first signs of itching and swelling."

D. Data Required for Evaluation

Guidelines for developing protocols for evaluating OTC orally administered drug products for the treatment of fever blisters. The Panel recognizes that currently there is not available a generally accepted protocol for the evaluation of the effectiveness of OTC orally administered drug products for the treatment of fever blisters. The Panel has reviewed carefully the published scientific literature and has not been able to find any well-controlled studies for these drugs. Further, the Panel has reviewed unpublished controlled studies undertaken for one of the sponsors of these drugs and has found these studies to be defective in one or more important facets. In order to move a Category III drug to Category I, successful, well-controlled studies must be performed. To aid investigators in designing these

tests of effectiveness, the Panel has developed the following guidelines. They are not meant to be definitive. There may be at present, or in the future, other appropriate techniques or improved methodologies not contained here. However, these guidelines illustrate the important issues that must be considered in clinical trials involving drugs for the treatment of fever blisters and, for that reason, should be an aid to investigators. The Panel suggests that deviations from these guidelines should be discussed with appropriate FDA personnel prior to initiation of a study.

1. *Objective of the study.* The primary objective is to determine whether the drug under investigation is more effective than a placebo in relieving the discomfort of fever blisters. "Relieving the discomfort" means relieving subjective symptoms such as pain, irritation, and itching. If a drug company desires to make a claim that the drug is effective in shortening the duration of fever blisters or in prolonging the interval between episodes, then the study objectives should include specific reference to such claims. The objectives should be stated in a complete and unambiguous manner.

2. *Target and sample population.* The target population consists of those individuals who develop fever blisters. The preferred sample population is those individuals who have frequent episodes of fever blisters (at least three times a year). Restriction to this sample population will increase the possibility that the study subjects will develop a fever blister during the study period. This would minimize the possibility of having individuals available for the study who do not develop fever blisters during the study.

If the drug is effective, it can be expected that its effectiveness will be demonstrated in the above sample population. If the drug is effective for these individuals, the Panel believes it would also be effective for the full target population.

For any particular study, the selected sample population should be specified fully, and pertinent characteristics should be described thoroughly.

3. *Study setting and investigators.* The study should be conducted by qualified investigators in clinical centers, academic settings, or private practices. The important component is the qualification of the investigator.

4. *Admissibility and exclusion criteria.* The study subjects must satisfy the criterion of the sample population, i.e., have frequent fever blisters (cold sores). In addition, the subjects:

a. Should be in good health,

b. Should have no known sensitivity to the test drug,

c. Should not be using other medications (including OTC medications), skin creams, or food products (e.g., milk products) which might influence the response of the subject in the study, and

d. Should be able to comprehend instructions and adhere to the study protocol (e.g., take the drug as required and report daily for examination as required).

5. *Variables to measure in the pre-episode period.* Prior to an episode of fever blisters, basic information on the subjects should be obtained. This is required not only to decide on admissibility into the study, but also to use as a reference point for evaluating efficacy. These variables should include:

a. Usual frequency, on a yearly basis, of episodes of fever blisters,

b. Usual areas of fever blisters,

c. Usual size of fever blisters,

d. Subjective evaluation of the usual discomfort from a fever blister on a 0 to 4 scale, with 0 representing no discomfort and 4 maximum discomfort (this scale should summarize all the components of discomfort such as itching, burning, irritation, and pain),

e. Usual time duration of fever blisters (both vesicular eruption and crusted stages),

f. Usual time duration of subjective discomfort, and

g. Events or situations that are associated with or precipitate an episode of a fever blister.

Other variables, such as age, sex, and health status of the subjects, that are routinely of interest in clinical studies, should also be collected at this time. Further, the distance of the subject from the clinical facility and the person's ability to come to the facility on a daily basis during an episode of a fever blister should be determined at this time.

6. *Study design.* The study must be randomized, double-blinded, and placebo-controlled. A parallel sample design appears to be preferred over a crossover design. A crossover design requires each study subject to have two separate episodes of fever blisters during the course of the study. This may require a long period of time and thus increases the potential for a substantial droupout rate. The parallel sample design requires only one occurrence of a fever blister per subject.

In the parallel sample design, subjects can be randomly assigned to one of two treatments (drug or placebo) at the initial interview. When a fever blister develops, the subject should record the time of first becoming aware of its impending development and should come to the investigator as soon as possible, definitely within the first 24 hours. At that time, the fever blister can be examined, and the subject can be given the appropriate treatment (drug or placebo), along with instructions for taking the treatment.

If a drug company is interested in investigating the effect of the drug on the length of time between episodes, a crossover design would be preferable.

7. *Duration of study from onset of the fever blister.* The length of the parallel sample study from onset of the fever blister should be at least 8 days. The average duration of an untreated fever blister is 10 to 14 days. The effectiveness of a treatment should be demonstrated by the eighth day. During the 8-day period the subject should be interviewed and examined daily by the investigator or an assistant.

8. *Variable to measure during the study.* At the first visit after onset, the lesion should be examined in detail to establish that it is in fact a fever blister. The time of day when the subject was first aware of it should also be recorded. Further, the subject should be interviewed to establish what events may have brought on the episode.

At all visits the subject should state on a scale of 0 to 4 a subjective evaluation of the discomfort from the fever blister experienced during the preceding 24 hours. As before, this scale should summarize all the components of discomfort such as itching, burning, irritation, and pain. Also, at all visits the lesion should be examined for physical characteristics, such as presence of vesicles, presence of dry crust, and size.

9. *Effectiveness measure.* The major effectiveness variable of the study is the subject's own subjective evaluation of the discomfort experienced from the fever blister. To establish effectiveness, comparisons of these evaluations for subjects on the drug should be made with those on the placebo. A time-series comparison over the 7 treatment days and/or separate comparisons for specific days (e.g., after 5 days) can be made. A drug company should be prepared to explain which comparisons are used to establish effectiveness.

If a claim of a reduction in the duration of an episode is desired, then investigation of the variable "number of days to healing of the fever blisters" will be needed for establishing this claim.

If a claim of a prolongation of the interval between episodes is desired, investigation of the variable "number of days to appearance of next lesion" will be needed to establishing the claim.

10. *Statistical tests and sample size.* Appropriate statistical tests should be

used to establish effectiveness. Sample sizes should be determined to give a p value of 0.05 or less for testing equality of effectiveness of the drug and placebo and a sufficiently small probability of error (e.g., 0.20) of not detecting a significant clinical superiority of the drug over the placebo. A drug company should be prepared to discuss what is meant by a significant clinical superiority.

11. *Number of clinical trials.* Two separate trials should be conducted by different investigators at different geographical sites. The samples from each of these sites should be representative of the sample population.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under 21 CFR 5.11 (see 46 FR 26052; May 11, 1981), the agency advises in this advance notice of proposed rulemaking that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations would be amended by adding in Part 357, a new Subpart H. to read as follows:

PART 357—MISCELLANEOUS INTERNAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart H—Orally Administered Drug Products for the Treatment of Fever Blisters

Sec.

357.701 Scope.
357.703 Definitions.
357.710 Orally administered active ingredients for the treatment of fever blisters. [Reserved]
357.750 Labeling of orally administered drug products for the treatment of fever blisters.

Authority: Secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371); secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704).

Subpart H—Orally Administered Drug Products for the Treatment of Fever Blisters

§ 357.701 Scope.

(a) An over-the-counter drug product for the treatment of fever blisters in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each condition in this subpart and each general condition established in § 330.1 of this chapter.

(b) References in this subpart to regulatory sections of the Code of Federal Regulations are to Chapter I of Title 21 unless otherwise noted.

§ 357.703 Definitions.

As used in this subpart:

(a) *Fever blisters.* Recurrent sores on the lips and other areas around the mouth, usually caused by herpes simplex virus. They are characterized by local tissue swelling followed by inflammation which evolve into vesicular eruptions, and then crust and fade.

(b) *Cold sores.* Fever blisters.

§ 357.710 Orally administered active ingredients for the treatment of fever blisters. [Reserved]

§ 357.750 Labeling of orally administered drug products for the treatment of fever blisters.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as a "fever blister treatment."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the phrase "for the relief of the discomfort of fever blisters (cold sores)."

(c) *Warnings.* The warning required by § 330.1(g) concerning overdoses is not required on orally administered active ingredients for the treatment of fever blisters.

(d) *Directions.* [Reserved]

Interested persons may, on or before April 5, 1982, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville MD 20857, written comments on this advance notice of proposed rulemaking. Three copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Comments replying to comments may also be submitted on or before May 5, 1982. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: September 23, 1981.

Arthur Hull Hayes, Jr.,

Commissioner of Food and Drugs.

Dated: December 17, 1981.

Richard S. Schweiker,

Secretary of Health and Human Services.

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